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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/622,487	08/17/2000	Shuji Sumida	0263-4047	7215

7590 01/03/2003

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EXAMINER	
RUSSEL, JEFFREY E	
ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 01/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/622,487	Applicant(s) SUMIDA ET AL.	
	Examiner Jeffrey E. Russel	Art Unit 1654	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,8,11 and 12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,8,11 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 August 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 1-5, 7, 8, 11, and 12 are rejected under 35 U.S.C. 103(a) as being obvious over Tsuji et al (U.S. Patent No. 5,202,117) in view of Michaelis et al (U.S. Patent No. 5,919,757). Tsuji et al teach an aqueous solution comprising equal amounts by weight of Polysorbate 80, a nonionic surfactant, and human G-CSF. The pH of the solution is 7. The solution is free from protein as a stabilizer. The solution is packaged in a vial. See column 8, line 56 - column 9, line 2. The source of the human G-CSF in Example 2 of Tsuji et al is Referential Example 2, in which recombinant G-CSF is produced by recombinant gene technology from transformed CHO cells (see column 5, lines 8-11 and 40-58). Michaelis et al teach that G-CSF produced in CHO cells is glycosylated (see column 2, lines 39-42). Tsuji et al do not teach the weight ratios recited in claims 3-5 and do not teach the pHs recited in claims 1 and 11. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal weight ratios and pHs for the compositions of the Tsuji et al because weight ratio and pH are art-recognized result-effective variables which are routinely determined and optimized in the pharmaceutical composition arts. The disclosure of Tsuji et al is not limited to any particular weight ratios or pHs, and slight deviations from the particular weight ratios and pHs disclosed in the examples of Tsuji et al does not impart patentability to composition claims in the absence of evidence of unexpected results.

3. Claims 1-5, 7, 8, 11, and 12 are rejected under 35 U.S.C. 103(a) as being obvious over the Japanese Patent Application 4-77436. (Citations in the rejection will be to the translation of the reference provided herein.) The Japanese Patent Application '436 teaches an aqueous

solution comprising equal amounts by weight of Polysorbate 80, a nonionic surfactant, and human G-CSF. The pH of the solution is 7. The solution is free from protein as a stabilizer. The solution is packaged in a vial. See page 10, Practical Example 2. The Japanese Patent Application '436 does not teach the use of glycosylated human G-CSF in this solution, although the Japanese Patent Application '436 at page 5, lines 5-19, does teach glycoproteins comprising human G-CSF and a sugar chain to be preferred human G-CSF. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to form a solution according to Practical Example 2 of the Japanese Patent Application '436 using a glycoprotein comprising human G-CSF and a sugar chain as the source of the human G-CSF because it is desirable to be able to prepare and store for use all known pharmaceutically active agents and because the Japanese Patent Application '436 teaches that a glycoprotein comprising human G-CSF and a sugar chain is a preferred source of the human G-CSF for the disclosed invention. With respect to instant claims 1, 3-5, and 11, practical Example 2 of the Japanese Patent Application '436 differs from these claims in the ratio of surfactant to G-CSF and in pH. However, it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal weight ratios and pHs for the compositions of the Japanese Patent Application '436 because weight ratio and pH are art-recognized result-effective variables which are routinely determined and optimized in the pharmaceutical composition arts. The disclosure of the Japanese Patent Application '436 is not limited to any particular weight ratios or pHs, and slight deviations from the particular weight ratios and pHs disclosed in the examples of the Japanese Patent Application '436 does not impart patentability to composition claims in the absence of evidence of unexpected results.

4. Applicant's arguments filed November 25, 2002 have been fully considered but they are not persuasive.

The obviousness rejections set forth in the previous Office action are maintained. Tsuji et al teach G-CSF compositions which are capable of being stored (see, e.g., column 9, line 1) and which are capable of being used to treat thrombi in mammals. Therefore, the G-CSF compositions of Tsuji et al must be sufficiently stable that they can be stored and that they can be used therapeutically. The examiner agrees with Applicants that there is no teaching either in Tsuji et al or in Michaelis et al that the G-CSF compositions of Tsuji et al are unstable. Applicants have also not presented any evidence that the G-CSF compositions of Tsuji et al are unstable, nor have Applicants presented any evidence that their claimed compositions are more stable than the compositions of Tsuji et al. Accordingly, there is no showing of unexpected results which would rebut the prima facie case of obviousness. A showing of unexpected results requires a comparison of Applicants' claimed invention with the closest prior art of record under the same test conditions. Applicants' Figures 1 and 2, and page 7, lines 15-18, do not test compositions having the same surfactant or having the same G-CSF:surfactant ratio as is taught in Tsuji et al's Example 2. Further, Applicants' Figures 1 and 2 and page 7, lines 15-18, include an additional component, D-mannitol, which is not present in Tsuji et al's Example 2. Given all these differences between the tests reported in Applicants' specification and figures and the composition taught in Tsuji et al's Example 2, it can not be concluded that Applicants' G-CSF compositions are more stable than Tsuji et al's compositions. At best, one might be able to conclude from these sections of Applicants' specification and figures that G-CSF in the presence of a D-mannitol stabilizer is more stable than G-CSF in the absence of a D-mannitol stabilizer;

however, this is an expected rather than an unexpected result. See MPEP 2144.05(II)(A); In re Boesch, 205 USPQ 215, 219 (CCPA 1980); and In re Mostovych, 144 USPQ 38, 42 (CCPA 1964); and Haynes Int'l, Inc. v. Jessup Steel Co., 28 USPQ2d 1652, 1655 n.3 (Fed. Cir. 1993) concerning prima facie obviousness and the optimization of weight ratios and pHs. Concerning Applicants' argument at page 4, first full paragraph, of the response, Tsuji et al already teach the claimed combination of ingredients - Example 2 of Tsuji et al does not contain any protein as a stabilizing ingredient. While Tsuji et al do disclose examples in which HSA is used as a stabilizer, its use is not required, and even a preferred embodiment does not teach away from a non-preferred embodiment. See In re Susi, 169 USPQ 423 (CCPA 1971). As far as the possible presence of mannitol as a stabilizing ingredient, Applicants' claims do not exclude this ingredient, and the compositions upon which Applicants' Figures 1 and 2 are based include this ingredient (see Table 1 and page 12, lines 15-19, of the specification). Patentability must be based upon claimed, not unclaimed, differences over the prior art.

The obviousness rejection based upon the Japanese Patent Application 4-77436 is maintained for reasons analogous to those set forth above with respect to Tsuji et al in view of Michaelis et al.

As discussed above, Applicants have not submitted any probative side-by-side comparison of the claimed invention with the closest prior art of record, and therefore have not established unexpected results for the claimed compositions. Tsuji et al's and the Japanese Patent Application '436's storage in the dark at less than 10°C suggests that the preparations were expected to be more stable at these conditions than at room temperature or in lighted conditions. Applicants' further inference, that "the preparations were not expected to be stable at

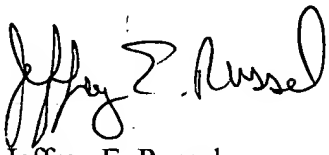
room temperature or above for extended storage", is unsupported. Finally, if the liquid preparations of the two references would have been inherently stable at or above 25°C, this would support the prima facie case of obviousness against the instant claimed compositions. Whether or not it would have been obvious to store the liquid preparations of the two references at 25°C or greater is irrelevant to the pending claims, none of which are drawn to a method of storage.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (703) 306-3220. The fax number for Art Unit 1654 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

January 2, 2003